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#43 Appeal Brief (3) 1/29/03 ec

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: John B. Harley, Judith A. James, and Kenneth M. Kaufman

Serial No: 09/500,904 Art Unit: 1648

Filed: February 9, 2000 Examiner: Foley, S.

For: DIAGNOSTICS AND THERAPY OF EPSTEIN-BARR VIRUS IN AUTOIMMUNE DISORDERS

Commissioner for Patents
Washington, D. C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 6-10 and 19-22 in the Office Action mailed May 8, 2002, in the above-identified patent application. A Notice of Appeal was filed on September 5, 2002. A Petition for an Extension of Time for two months, up to and including January 5, 2003, and the appropriate fee for a small entity are enclosed. The fee for the filing of this Appellants' Brief is also enclosed.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignees, the Oklahoma Medical Research Foundation, Oklahoma City, OK, The Board of Regents of the University of Oklahoma Health Science Center, Oklahoma City, OK, and the licensee, JK Autoimmunity, Inc., Oklahoma City, OK.

(2) RELATED APPEALS AND INTERFERENCES

The following related appeals are known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which may have a bearing on the Board's decision in this appeal:

U.S.S.N. 08/475,955 filed June 7, 1995. A copy of the decision in this application was placed in this file. The examiner questioned the relevance, but the undersigned believes that the technology is related and issues on appeal are related. U.S.S.N. 08/475,955 is drawn to the discovery of the viral peptides that elicit an autoimmune reaction in the patient, that leads to lupus. The claims in this case are drawn to a diagnostic method which can use these peptides as antigen to measure levels of antibodies indicative of autoimmune disease.

U.S.S.N. 08/781,296 filed January 13, 1997 by John B. Harley and Judith A. James entitled "Diagnostics and Therapy of Epstein-Barr Virus in Autoimmune Disorders", of which this is a continuation-in-part has been on appeal. The examiner recently changed and prosecution was reopened. It is possible the case will be back on appeal since the new office action reiterated the rejections on appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 6-10 and 19-22 are pending and on appeal. The text of each claim on appeal, as amended, is set forth in the Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The pending claims were last amended by the Amendment mailed June 28, 2001.

(5) SUMMARY OF THE INVENTION

Differences have been identified in the immune responses to Epstein-Barr infection between individuals who develop a specific autoimmune disease and those who do not. (page 8, lines 20-22). These differences are used in the claimed diagnostic assay kits and methods of use thereof to distinguish those who are at greater risk for developing specific autoimmune diseases from those who are a lesser risk. (page 8, lines 22-24) Individuals who are not at as great a risk for developing autoimmune disease can be identified by reactivity to various peptides, for example, as demonstrated in the examples where individuals who are not prone to develop lupus are characterized by antibodies to GAGAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO: 7). (page 2, lines 15-19) Subsets of antigenic peptides can be used to identify patients at risk for particular clinical manifestations or patients in particular prognostic groups. (page 26, lines 21-23) The peptides can be used in combination in assays, such as the solid phase assay, to classify patients. (page 26, lines 23-24)

(6) ISSUES ON APPEAL

The issues presented on appeal are

(1) whether claims 6-10 and 19-22 are definite under 35 U.S.C. 112, second paragraph.

(2) whether claims 6-10 and 19-22 comply with the written description and/or enablement requirement under 35 U.S.C. 112, first paragraph.

Claims 6-10 and 19-22 were provisionally rejected under the doctrine of obviousness-type double patenting over claim 35 of U.S.S.N. 08/781,296. This rejection will be addressed

either by filing of an appropriate Terminal Disclaimer or by cancellation of claim 35 in the co-pending application, once the claims have otherwise been determined to be allowable.

(7) GROUPING OF CLAIMS

The claims do not stand or fall together, as discussed in more detail below.

(8) ARGUMENTS

(i) The Invention

Differences have been identified in the immune responses to Epstein-Barr infection between individuals who develop a specific autoimmune disease and those who do not. These differences are used to distinguish those who are at greater risk for developing specific autoimmune diseases from those who are a lesser risk. For example, individuals who are not at as great a risk for developing autoimmune disease can be identified by reactivity to the various peptides, for example, as demonstrated in the examples where individuals who are not prone to develop lupus are characterized by antibodies to GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO: 7). Other structures derived from Epstein-Barr virus can be used to predict who will develop autoimmune disease. These structures were identified using standard techniques, the known sequences of the Epstein-Barr viral proteins and the known sequences of the autoantigens such as Sm B' and Ro/SSA, and sera from many patients, including a large data base that spanned a number of years in the same patients, allowing the appellants to follow the progression of the disease and markers for the disease, over a period of years. Comparison with normals or individuals who did not develop the disease allow those skilled in the art to identify individuals who are more likely than not to develop autoimmune disease.

The claims are drawn to the following:

Claim 6 defines a diagnostic assay or test for predicting the risk of developing lupus as including the following reagents:

(1) reagents which can be used to detect in a patient sample materials which are indicative of Epstein-Barr viral infection:

(a) levels of antibodies to Epstein-Barr virus,

(b) levels of indicators of Epstein-Barr infection of cells, or

(c) levels of Epstein-Barr DNA or protein in a patient, and

(2) control samples from individuals not at risk of developing lupus, and

(3) means for determining the differences in the levels of a patient and control samples to distinguish individuals at higher risk of developing lupus from those at lower risk of developing lupus.

Claim 7 further defines the reagents of claim 6 for use in particular types of assays: assays based upon the relative presence of an antibody, assays based on cellular proliferation, assays based on molecular binding, assays based on cytokine production, assays based on skin reaction, and assays based on cell surface antigen.

Claim 8 limits the reagents to specific peptides used to detect antibodies, PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2), RGRGREK (SEQ ID NO:3), GAGAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), GPQRRGGDNHGRGRGRGRGGGRPG (SEQ ID NO:98), GGSGSGPRHRDGVRRPQKRP (SEQ ID NO:25), RPQKRPSC (SEQ ID NO:26), QKRPSCIGCKGTHGGTG (SEQ ID NO:27), GTGAGAGARGRGG (SEQ ID NO:99), SGGRGRGG (SEQ ID NO:100), RGGSGGRRGRGR (SEQ ID NO:101), RARGRGRGRGEKRPRS (SEQ ID NO:102), SSSSGSPPRRPPPGR (SEQ

ID NO:103), RPPPGRRPFFHPVGEADYFEYHQEG (SEQ ID NO:104), PDVPPGAI (SEQ ID NO:33), PGAIEQGPA (SEQ ID NO:34), GPSTGPRG (SEQ ID NO:105), GQGDGGRRK (SEQ ID NO:37), DGGRRKKGGWFGKHR (SEQ ID NO:38), GKHRGQGGSN (SEQ ID NO:106), GQGGSNPK (SEQ ID NO:107), NPKFENIA (SEQ ID NO:108), RSHVERTT (SEQ ID NO:109), VFVYGGSKT (SEQ ID NO:110), GSKTSLYNL (SEQ ID NO:111), GMAPGPGP (SEQ ID NO:46), PQPGPLRE (SEQ ID NO:47), CNIRVTVC (SEQ ID NO:48), RVTVCSFDDG (SEQ ID NO:49), PPWFPPMVEG (SEQ ID NO:50).

Claim 9 limits the assay of claim 8 to a specific peptide which is predictive of an individual not developing lupus, GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7).

Claim 10 defines the assay as useful for testing patients identified with or at risk of developing systemic lupus erythematosus comprising control samples from individuals with systemic lupus erythematosus (in addition to controls who do not have lupus).

Claims 19-22 define methods paralleling the limitations of the diagnostic assay of claims 6-10.

Claim 19 defines a method for determining the likelihood that an individual has lupus induced by Epstein-Barr virus, or is at risk for developing lupus, including the steps of:

(1) obtaining a sample from the individual to be tested,

(2) mixing the sample with reagents which can be used to detect levels of

(a) antibodies to Epstein-Barr virus,

(b) indicators of Epstein-Barr infection of cells, or

(c) levels of Epstein-Barr DNA or protein in a patient,

(3) analyzing the sample, and

(4) comparing the analysis of the sample with results obtained with control samples from individuals not at risk of developing lupus to determine if the differences in levels of the individual and control samples indicates the individual is at a higher risk of developing lupus than controls who are at lower risk of developing lupus.

Claim 20 parallels claim 7. Claims 21 and 22 define the same peptides as claims 8 and 9.

The methods defined by these claims are fully supported by several actual working examples in the specification, showing that the claimed method is predictive of the likelihood one will or will not develop an autoimmune disease such as lupus.

Example 1 is a study to determine which of 233 overlapping octapeptides in an autoantigen, Sm B', are indicative of disease. As shown by Figure 2, all of the anti-Sm sera (i.e., from patients with lupus) tested bound almost the identical octapeptide structures. As demonstrated by the data in the example, anti-Sm sera binds to PPPGMRPP and structurally similar sequences (Figure 3 SEQ ID NO:4). These sequences included PPPGRRP (SEQ ID NO:1), which is found in the Epstein-Barr Nuclear Antigen-1 (EBNA-1) protein. GRGRGRGG (SEQ ID NO:2) and RGRGREK (SEQ ID NO:3) are also sequences from Epstein-Barr virus Nuclear Antigen-1, but these are similar to a major antigenic epitope of Sm D in lupus patients, GRGRGRGRGRGRGRGRGRGGPRRR (SEQ ID NO:9). All three peptides bind at least three times more antibody from the anti-Sm precipitin positive lupus patient sera than the controls. The antibody binding to these peptides in the lupus patient sera was over half of the antibody binding level found for PPPGMRPP (SEQ ID NO:4).

Data was also obtained using a collection of about 80,000 specimens from 26,000 individuals collected and stored over a period of 17 years. This Clinical Immunology database

was screened to identify lupus patients who developed anti-Sm under observation. The clinical serum bank was found to contain stored serum specimens from 161 patients with anti-Sm antibodies in at least one serum sample. Four patients were identified among these who, during their SLE clinical course or after initial presentation, converted from being precipitin negative to precipitin positive for antibodies to Sm. Sera from each individual were retrieved from before and after the development of anti-Sm antibodies. For each serum sample, antibody levels were tested by ELISA for binding to Sm and the Sm/nRNP complex. The Ro protein was selected as a control antigen since none of the four patients demonstrated anti-Ro antibodies by Oüchterlony immunodiffusion. Each patient increased binding towards the Sm and Sm/nRNP antigens over time, without an increase in binding to the Ro protein (above background levels) by ELISA. Anti Sm B/B' indicated specificity was confirmed by Western blotting. Binding to Sm B/B' indicated acquisition of a new antibody specificity, since binding to this protein was not detected in the first available sample tested from each patient. Each available serum sample was tested for antibody binding to the 233 overlapping octapeptides of Sm B/B'. Each patient had antibodies which initially targeted the proline rich, repeated motif, PPPGMRP(G)P (SEQ ID NO:4). With time the response diversified to other regions of Sm B/B' when additional serum samples were available.

Sm positive patients from whom a serum sample was available from presentation were also screened. Serum samples from lupus patients stored early in the course of the disease process bind only PPPGMRPP (SEQ ID NO:4) (and neighboring peptides) of the 233 possible octapeptides of B/B', as shown by Figure 4 for one such patient. In addition to the patient presented in Figure 4, two others who initially had a simplified pattern of octapeptide binding

were identified. In all three of these cases, only PPPGMRPP (SEQ ID NO:4) and PPPGMRGP (SEQ ID NO:8) were bound and no other octapeptide were bound. All other anti-Sm positive sera tested bind these octapeptides as well as others. These results are consistent with PPPGMRPP (SEQ ID NO:4) and PPPGMRGP (SEQ ID NO:8) being the first epitopes of the Sm B/B' autoantigen (Arbuckle, M. R., et al., Scan. J. Immunol. 50:447-55, 1999). This repeated PPPGMRPP (SEQ ID NO:4) motif is an early target in three additional patients tested from whom sera were available from early in their disease. In all of these patients PPPGMRPP (SEQ ID NO:4) is the first autoimmune epitope of the Sm B/B' autoantigen against which one can detect antibody binding.

Four peptide sequences from Epstein-Barr virus were separately evaluated for binding to sera from patients with an autoimmune disease (Figures 3 and 7). All are found in the EBNA-1 (Epstein-Barr virus Nuclear Antigen-1) protein. Subjects with an autoimmune disease, systemic lupus erythematosus, have higher levels of antibodies against PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2) and RGRGREK (SEQ ID NO:3) than do normal controls. On the other hand the glycine-alanine repeat sequence, GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), which, after infection by Epstein-Barr virus, is a major epitope in infectious mononucleosis and in normals (Rhodes, G. et al. J. Exp. Med. 165:1026-1040 (1987)) tends not to be bound by patients with lupus (Figure 7). Figure 7 is a graph of the binding to the peptide GAGAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7) from Epstein-Barr virus Nuclear Antigen-1 by lupus sera who all had anti-Sm and anti-nRNP precipitins, as compared to normal control sera. The structures (octapeptides from Epstein-Bar virus nuclear antigen-1) bound by the lupus sera tested is listed in Table 8. These are taken from epitopes with average binding

greater than 3 standard deviations about the normal mean (of EBV positive normal controls) and commonly bound by patient sera with an O.D. greater than 0.45 absorbence units. Sequences longer than eight amino acids represent neighboring octapeptides that exceed the 0.450 A U.

Other sequences have also been identified. As described by Example 10, PPPGMRPP (SEQ ID NO:4) constructed on a multiple antigenic peptide (MAP) backbone was coupled to CNBr activated Sepharose™. Each MAP molecule contains eight copies of the PPPGMRPP (SEQ ID NO:4) peptide on a branching polylysine backbone. One ml of sera from a Sm precipitin positive black female lupus patient was passed over the column and extensively washed. Bound antibodies were removed with 3 M guanidine and then dialyzed against 25 mM Tris-HC1 pH 8.0. The column affinity purification was repeated using the first round bound material. Purified antibodies were concentrated and quantitated by UV absorption. In order to identify the peptide epitopes recognized by human anti-PPPGMRPP (SEQ ID NO:4) antibodies, a random heptapeptide phage display library from New England Biolabs (Bar Harbor, MA) was screened. A heptapeptide library was selected because all 1.28×10^9 seven amino acid possibilities could be represented (8 a.a.= 2.56×10^{10} combinations, 9 a.a. = 5.12×10^{11} combinations). In this library each random heptapeptide is expressed at the N-terminus of the pIII minor phage coat protein followed by a Gly-Gly-Gly spacer. There is on average five copies of the pIII protein per phage particle. Theoretically, every combination of seven amino acid sequences could be expressed. Antibody-phage complexes were isolated by incubation with protein-A agarose. Following the fourth round of amplification, 70 clones were isolated and sequenced (Table 9). Eleven distinct sequence motifs were identified. Both class I and class II motifs share obvious homology to PPPGMRPP (SEQ ID NO:4) peptide. The binding of anti-

PPPGMRPP (SEQ ID NO:4) antibodies to the different types of peptides displayed on the phage was then characterized. Figures 8A-E are graphs of the binding to the overlapping octapeptides from Epstein-Barr virus Nuclear Antigen-1. The binding of three controls are presented in Figures 8A, 8B and 8C and that of two lupus sera in Figures 8D and 8E. Figure 8A is from a normal who has no evidence of having been infected by Epstein-Barr virus by the assay for anti-Epstein-Barr virus Viral Capsid Antigen IgG. The other sera presented (Figures 8B through 8E) are all positive in this assay. The peptides presented had average reactivity at least 3 standard deviations above the normal mean. Sequences longer than eight amino acids represent neighboring octapeptides that exceed the 0.450 A.U. threshold.

In summary, appellants have identified a number of specific peptides that can be used to one can identify patients very early in the disease, based on reactivity with these specific peptides.

Example 9 demonstrates that one can screen for the antibodies using cell line lysates rather than the peptides. Three different cell lines: B95 (marmoset cell line with the most common strain, EBV-1 or –A), Jiyoye cell line (from Burkitt's lymphoma with EBV-2 or –B), and the Ramos cell line which has no EBV infection were obtained. 15 patient and 13 control sera were screened for binding to these different cells lysates. Anti-EBNA-1 is quite obvious as an approximate 70 kD band. All 15 patient sera, as well as 11 of 13 control sera, strongly bind the EBNA-1 protein in both strains. An EBNA-1 monoclonal antibody confirms the identify of this band. Many other proteins are bound by patient and control sera, however there appears to be more patient sera binding to approximately 90 kD, 58 kD, 50 kD, and 36 kD bands.

In summary, the claims define a diagnostic kit and method of use for determining the likelihood that an individual will develop an autoimmune disease. As the examples demonstrate, these assays, and reagents for use therein, have been made, tested, and demonstrated to yield statistically significant results.

(ii) Rejection Under 35 U.S.C. § 112, second paragraph

Claims 6-10 and 19-22 were rejected as indefinite. The basis of the rejection appears to be that the examiner believes that the phrase "means for determining" "does not correlate with the objective to 'predict the risk of developing lupus'" in the preamble.

There are two groups of claims that must be considered separately: claims 6-10, drawn to a diagnostic assay (or kit) which contains reagents for use in the method of claims 19-22. The consideration with respect to claim 6 is whether or not one skilled in the art of diagnostic assays, in view of the specification, would know what is meant by means for determining the differences in:

(a) levels of antibodies to Epstein-Barr virus,

(b) levels of indicators of Epstein-Barr infection of cells, or

(c) levels of Epstein-Barr DNA or protein in a patient, and

of a patient and control samples from individuals not at risk of developing lupus to distinguish individuals at higher risk of developing lupus from those at lower risk of developing lupus.

As discussed above, there are numerous actual working examples in the application which describe the isolation of antibodies, infected cell lysates, specific peptides, and Epstein-Barr DNA, from patient and control sera, and comparisons thereof, with statistical significance.

The examiner's only justification for the rejection has to do with "risk factors for distinguishing whether a subject will develop lupus or whether a subject has a chance of developing lupus has not been established by the claimed assay". This is irrelevant to a rejection for definiteness or lack thereof. The only issue is whether or not one skilled in the art would be able to determine the scope and meaning of the claim. The examiner has provided no rationale nor pointed to any evidence of why someone skilled in the art would be unable to do so.

The rejection has even less merit as to the dependent claims, defining the reagents as specific peptides (claims 8, 9, 21 and 22) which have been shown to be associated with disease or the absence thereof (the peptide of claims 9 and 22), specific types of assays (claims 7 and 20), and where there is a positive control sample from a patient with lupus.

The examiner has provided no argument as to why the dependent claims, describing assays that have actually been reduced to practice and demonstrated to yield statistically significant results, are not definite. It is well established that the patentability of each claim should be separately examined. The examiner has failed to do so.

In summary, all claims 6-10 and 19-22 are definite as required by 35 U.S.C. 112, second paragraph.

(iii) Rejection Under 35 U.S.C. § 112, first paragraph

Claims 6-10 and 19-22 were rejected under 35 U.S.C. 112, first paragraph. It is not clear if the rejection is being made on the basis that the claims lack written description, lack utility, lack enablement or some hybrid thereof. Therefore each aspect is discussed below.

(a) The legal requirements under 35 U.S.C. 101 and 112, first paragraph

An invention must have utility. This requirement can be found in U.S.C. § 101 which states," Whoever invents or discovers any new and *useful* process or . . . composition of matter . . . may obtain a patent . . ." (emphasis added). This requirement is also implicitly found in 35 U.S.C. § 112 which requires the specification to provide a written description for "making and *using*" the claimed subject matter.

Whether the utility requirement comes from 35 U.S.C. § 101 or 35 U.S.C. § 112, the standard to be applied is the same. *Ex parte Maas*, 14 USPQ2d 1762, 9 USPQ2d 1746, 1747 (Bd. Pat. App. & Int'f 1987). The *Maas* court stated, "the issue under 35 U.S.C. § 112 relating to an enabling disclosure is subsumed within the issue under 35 U.S.C. § 101 relating to patentable utility." Any analysis of a claim under 35 U.S.C. § 112, first paragraph relating to the use of the claimed subject matter, need only meet the standards of the utility requirement of 35 U.S.C. § 101 because if the claimed subject matter meets the utility requirement it is presumed to meet the enablement requirement of use.

To meet the utility requirement the invention must simply have a "practical utility" in the "real world sense." (*Nelson v. Bowler*, 626 F.2d 853, 856 (CCPA, 1980)). Any use which gives immediate benefit to the public is sufficient to be a "practical utility". *Id.* at 856. It is clear that for an invention to have "practical utility" it must be operative. However, to fail the utility requirement the claimed subject matter must be "totally incapable of achieving a useful result. ("In short, the defense of non-utility cannot be sustained without proof of total incapacity.").) (*Brooktree Corp v. Advanced Micro Devices. Inc.*, 977 F.2d 1555 (Fed. Cir. 1992). See also *E.I. du Pont De Nemours and Co. v. Berkley and Co.*, 620 F.2d 1247, 1260 n.17, 205 USPQ 1, 10 n.17 (8th Cir. 1980). An

assertion of utility is sufficient to meet the utility requirement unless the assertion is "incredible in the light of the art or factually misleading." (*In re Citron*, 325 F.2d 1389 (CCPA, 1963)).

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*See, e.g.*, Genentech, Inc. v. Novo Nordisk A/S, 108 F3d at 165, 42 USPQ2d at 1004 (quoting In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also In re Fisher, 427 F.2d at 839, 166 USPQ at 24; United States v. Telectronics, Inc., 857 F.2d 778 (Fed. Cir. 1988); In re Stephens, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (M.I.T. v. A.B. Fortia, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether making or using the invention would have required undue experimentation, and thus whether the disclosure is enabling, is a legal conclusion based upon several underlying factual inquiries. See In re Wands, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in Wands, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement

obviously varies inversely with the degree of unpredictability of the factors involved." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' Atlas Powder Co., v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

> The test is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.
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> Ex parte Jackson, 217 USPQ 804, 807 (1982)

As stated in the MANUAL OF PATENT EXAMINING PROCEDURE §2164.04 (7th ed. 1998), *citing* In re Wright, 999 F.2d 1557, 1562 (Fed. Cir. 1993), the examiner has the initial burden to establish a reasonable basis to question the enablement of the application.

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must be taken as being in compliance with the enablement requirement** of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.
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> *Id.* at § 2164.05 (emphasis added).

Lastly, there is no legal requirement that an inventor have actually reduced the invention to practice prior to filing. MPEP at § 2164.02, *citing* Gould v. Quigg, 822 F.2d 1074 (Fed. Cir. 1987). "The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." *Id.*

The first paragraph of 35 U.S.C. § 112 sets forth the written description requirement for patents as follows:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

The standard regarding what is or is not supported by the specification has been clearly articulated as "requiring the specification to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, the inventor was in possession of the invention", i.e., whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111, 1117 (Fed . Cir. 1991). Compliance with the written description requirement is essentially a fact-based inquiry that will "necessarily vary depending on the nature of the invention claimed." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991) (citing *In re DiLeone*, 436 F.2d 1404, 1405 (CCPA 1971)). Satisfaction of the written description requirement is determined on a case-by-case basis.

The inquiry into whether or not there is an adequate written description is not performed in a vacuum. "Knowledge of one skilled in the art is relevant to meeting [the written description] requirement." *Enzo Biochem, Inc. v. Gen-Probe*, Docket No. 01-1230 (Fed. Cir. Apr. 2, 2002) (slip op.). This fact has implications not only for validity challenges, but also for patent prosecution. *See In re Alton*, 76 F.3d 1168, 1174-75 (Fed. Cir. 1996).

In the most recent CAFC decision, *Enzo Biochem, Inc. v. Gen-Probe*, Docket No. 01-1230 (Fed. Cir. July 15, 2002), the Federal Circuit vacated a prior decision, *Enzo Biochem, Inc. v. Gen-Probe*, 285 F.3d 1013, 62 USPQ 2d 1289 (Fed. Cir. April 2, 2002), and reversed the district court's grant of summary judgment that Enzo's claims are invalid for failure to meet the written description requirement, stating in relevant part:

"It is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement. The PTO has issued Guidelines governing its internal practice for addressing that issue. The Guidelines, like the Manual of Patent Examining Procedure ("MPEP"), are not binding on this court, but may be given judicial notice to the extent they do not conflict with the statute. See Molins PLC v. Textron, Inc., 48 F.3d 1172, 1180 n.10, 33 USPQ2d 1823, 1828 n.10 (Fed. Cir. 1995). In its Guidelines, the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Guidelines, 66 Fed. Reg. at 1106 (emphasis added). For example, the PTO would find compliance with § 112, ¶ 1, for a claim to an "isolated antibody capable of binding to

antigen X," notwithstanding the functional definition of the antibody, in light of "the art-recognized method of making antibodies *to fully characterized antigens*, the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the *antibody technology is well developed and mature.*" (emphasis added) Synopsis of Application of Written Description Guidelines, at 60, available at http://www.uspto.gov/web/patents/guides.htm ("Application of Guidelines").

The PTO Guidelines clearly state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Guidelines, 66 Fed. at 1106." (emphasis added) *Enzo Biochem, Inc. v. Gen-Probe*, Docket No. 01-1230 (Fed. Cir. July 15, 2002).

The general principle of the written description requirement for a claimed genus may be satisfied through (1) sufficient description of a representative number of species by actual reduction to practice, (2) reduction to drawings of a general structure, or (3) disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, (4) describing functional characteristics coupled with a known or disclosed correlation between function and structure, or (5) a combination of such identifying characteristics, sufficient to show the appellant was in possession of the claimed genus. Reagents of the University of California v. Eli Lilly, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

(b) The claims comply with 35 U.S.C. 112, first paragraph

Appellants have met these legal requirements. As discussed above, the application contains a number of examples that show that one can differentiate between samples of patients with lupus and controls that do not have lupus, both prior to development of symptoms as well as after development of symptoms. These examples demonstrate that specific peptide sequences have been obtained which can be used to screen sera from patients for antibodies which bind to the peptides, some of which are indicative of disease (to a degree that there is 300% more binding from those with or developing disease as compared to negative controls) and some of which are indicative that a patient will not develop disease (the peptide of claims 9 and 22). The examples also demonstrate that assays using cell lysates in functional assays (as defined by claims 7 and 20) can show differences between the two groups, as well as assays for Eppstein-Barr DNA. These examples are not hypothetical. They are based on actual patient samples. There are two groups of patients - those being tested after they have developed the symptoms of the disease and those for whom samples are available both before and after development of symptoms. The assay has been shown to be predictive with these samples as well - demonstrating that appellants had in their possession no later than the date of filing of this application, the claimed diagnostic assay and method of use thereof, that they had described the assay and method of use thereof in sufficient detail to enable anyone of skill in the art to make and use the claimed assay and method, and that the method had utility.

Claim 1 recites:

A diagnostic test to predict the risk of developing lupus comprising

(1) reagents which can be used to detect levels of antibodies to Epstein-Barr virus, indicators of Epstein-Barr infection of cells, or levels of Epstein-Barr DNA or protein in a patient, and

(2) control samples from individuals not at risk of developing lupus, and

(3) means for determining the differences in levels of a patient and control samples to distinguish individuals at higher risk of developing lupus from those at lower risk of developing lupus.

Those skilled in the art would have no trouble interpreting this claim. It represents a very standard assay, although the specific (rather than general) reagents and desired goal are not typical.

The test contains reagents such as antibodies to EBV antibodies, EBV proteins, or proteins which are known indicators of EBV infection; control samples which are used to eliminate "background" reactions with the reagents not indicative of developing lupus; and means for distinguishing the background reactions (i.e., the reactions between the reagents and the control samples) and the patient samples. If the reaction is greater with the patient sample than with the controls, the patient is at risk. The means are standard - in some cases, the means may be an ELISA assay, where a colored reaction is titered to quantitate the number of reactants; it may be a chromatographic assay where a spectrophotometer is used to measure the intensity of the reaction; it may be an immunoprecipitation assay; This is certainly a relative analysis, but one commonly practiced by those skilled in the art. Who has not had a blood analysis in which each determination is followed by the normal range, so that one can determine whether one is within the normal range or outside the normal range, and therefore at a great risk?

Claims 6-10 and 19-22 have been rejected apparently for use of the term "likelihood" and "at risk". The terms are well known to those skilled in the art. Particularly in a case such as

lupus, where there is a genetic component (same as in some types of cancer or heart disease), there are tests that can be performed to indicate if an individual is more likely than the average individual to develop a disorder, in this case, lupus. Contrary to the examiner's assertion that a cause-and-effect must be established between EBV and lupus before one can claim an assay, this is not the legal standard. The test is whether or not the test yields a more probable than not outcome - which is all many physicians require before initiating far more expensive and comprehensive testing which would be more definitive.

No more is required under 35 U.S.C. 112, first paragraph. There is no legal requirement to "conclusively" correlate evidence that EBV cause autoimmune disease - the claims are drawn only to an assay and method of predicting the likelihood that a patient will develop the disease. This appellants have shown, using samples obtained from patients and negative controls prior to and after development of disease. Moreover, appellants have described these assays in sufficient detail to enable one skilled in the art, without undue experimentation, to practice the same assays, using the same reagents as claimed. The examiner has provided no evidence to the contrary. All that has been cited in support of the rejection is that the prior art does not establish that the claimed assay and method is useful. This, of course, is not the test under 35 U.S.C. 112.

Moreover, the examiner has completely failed to examine the dependent claims. No rationale is provided for why claims drawn to specific peptides, peptides shown to have reactivity predominantly with patient or control sera, both before and after development of disease, are not in compliance with 35 U.S.C. 112, first paragraph.

In summary, claims 6-10 and 19-22 meet the requirements under 35 U.S.C. 112, first paragraph.

(9) SUMMARY AND CONCLUSION

Based on the foregoing, the compositions of claims 6-10 and methods of claims 19-22 are definite, enabled, comply with the written description requirement, and have utility.

Respectfully submitted,

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CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this , along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: January 6, 2003

Rivka D. Monheit

APPENDIX: Claims on Appeal

6. A diagnostic test to predict the risk of developing lupus comprising

reagents which can be used to detect levels of antibodies to Epstein-Barr virus, indicators of Epstein-Barr infection of cells, or levels of Epstein-Barr DNA or protein in a patient, and

control samples from individuals not at risk of developing lupus, and

means for determining the differences in levels of a patient and control samples to distinguish individuals at higher risk of developing lupus from those at lower risk of developing lupus.

7. The diagnostic test of claim 6 wherein the reagents are used in assays selected from the group of assays based upon the relative presence of an antibody, assays based on cellular proliferation, assays based on molecular binding, assays based on cytokine production, assays based on skin reaction, and assays based on cell surface antigen.

8. The diagnostic test of claim 6 wherein the reagents used to detect antibodies to peptides from Epstein-Barr virus are selected from the group consisting of PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2), RGRGREK (SEQ ID NO:3), GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), GPQRRGGDNHGRGRGRGRGGGRPG (SEQ ID NO:98), GGSGSGPRHRDGVRRPQKRP (SEQ ID NO:25), RPQKRPSC (SEQ ID NO:26), QKRPSCIGCKGTHGGTG (SEQ ID NO:27), GTGAGAGARGRGG (SEQ ID NO:99), SGGRGRGG (SEQ ID NO:100), RGGSGGRRGRGR (SEQ ID NO:101), RARGRGRGRGEKRPRS (SEQ ID NO:102), SSSSGSPPRRPPPGR (SEQ ID NO:103), RPPPGRRPFFHPVGEADYFEYHQEG (SEQ ID NO:104), PDVPPGAI (SEQ ID NO:33), PGAIEQGPA (SEQ ID NO:34), GPSTGPRG (SEQ ID NO:105), GQGDGGRRK (SEQ ID NO:37), DGGRRKKGGWFGKHR (SEQ ID NO:38), GKHRGQGGSN (SEQ ID NO:106), GQGGSNPK (SEQ ID NO:107), NPKFENIA (SEQ ID NO:108), RSHVERTT (SEQ ID NO:109), VFVYGGSKT (SEQ ID NO:110), GSKTSLYNL (SEQ ID NO:111), GMAPGPGP (SEQ ID NO:46), PQPGPLRE (SEQ ID NO:47), CNIRVTVC (SEQ ID NO:48), RVTVCSFDDG (SEQ ID NO:49), PPWFPPMVEG (SEQ ID NO:50).

9. The diagnostic test of claim 8 comprising reagents for detection of antibodies to GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7).

10. The diagnostic test of claim 6 for testing patients identified with or at risk of developing systemic lupus erythematosus comprising control samples from individuals with systemic lupus erythematosus.

19. A method for determining the likelihood that an individual has lupus induced by Epstein-Barr virus, or is at risk for developing lupus, comprising

obtaining a sample from the individual to be tested,

mixing the sample with reagents which can be used to detect levels of antibodies to Epstein-Barr virus, indicators of Epstein-Barr infection of cells, or levels of Epstein-Barr DNA or protein in a patient,

analyzing the sample, and

comparing the analysis of the sample with results obtained with control samples from individuals not at risk of developing lupus to determine if the differences in levels of the individual and control samples indicates the individual is at a higher risk of developing lupus than controls who are at lower risk of developing lupus.

20. The method of claim 19 wherein the reagents are used in assays selected from the group of assays based upon the relative presence of an antibody, assays based on cellular proliferation, assays based on molecular binding, assays based on cytokine production, assays based on skin reaction, and assays based on cell surface antigen.

21. The method of claim 19 wherein the reagents used to detect antibodies to peptides from Epstein-Barr virus are selected from the group consisting of PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2), RGRGREK (SEQ ID NO:3), GAGAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), GPQRRGGDNHGRGRGRGRGGGRPG (SEQ ID NO:98), GGSGSGPRHRDGVRRPQKRP (SEQ ID NO:25), RPQKRPSC (SEQ ID NO:26), QKRPSCIGCKGTHGGTG (SEQ ID NO:27), GTGAGAGARGRGG (SEQ ID NO:99), SGGRGRGG (SEQ ID NO:100), RGGSGGRRGRGR (SEQ ID NO:101), RARGRGRGRGEKRPRS (SEQ ID NO:102), SSSSGSPPRRPPPGR (SEQ ID NO:103), RPPPGRRPFFHPVGEADYFEYHQEG (SEQ ID NO:104), PDVPPGAI (SEQ ID NO:33), PGAIEQGPA (SEQ ID NO:34), GPSTGPRG (SEQ ID NO:105), GQGDGGRRK (SEQ ID NO:37), DGGRRKKGGWFGKHR (SEQ ID NO:38), GKHRGQGGSN (SEQ ID NO:106),

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22. The method of claim 19 wherein the individual is tested for the presence of antibodies to GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7).

TABLE OF CONTENTS

ATL1 #538648 v1